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APPLICATION NUMBER: 60/424,978

FILING DATE: November 08, 2002

RELATED PCT APPLICATION NUMBER: PCT/US03/28742



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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

Express Mail Label No.

ET899942962US

INVENTOR(S)

Given Name (first and middle (if any))	Family Name or Surname	Residence (City and either State or Foreign Country)
Hartmut M.	Hanauske-Abel	Edgewater, New Jersey
Anthony	Popowicz	New York, New York
Edith	Wolff	Bethesda, Maryland

☒ Additional inventors are being named on the 1 separately numbered sheets attached hereto

TITLE OF THE INVENTION (500 characters max)

Small Molecule Ligands Of Eukaryotic Translation Initiation Factor 5A (eIF-5A) and Their Use to Control Proliferation Of Cells.

Direct all correspondence to:

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ENCLOSED APPLICATION PARTS (check all that apply)

☒ Specification Number of Pages

4

☐ CD(s), Number

☒ Drawing(s) Number of Sheets

7

☒ Other (specify)

Claims (1 pg); Post Card

☐ Application Data Sheet. See 37 CFR 1.76

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☒ Applicant claims small entity status. See 37 CFR 1.27.

☐ A check or money order is enclosed to cover the filing fees

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☐ No.

☒ Yes, the name of the U.S. Government agency and the Government contract number are:

R01CA42908

NIH Grant Number:

Respectfully submitted,

SIGNATURE

Margaret Mary Kozik Richardson

Date 11/08/2002

TYPED or PRINTED NAME Margaret Mary Kozik Richardson

REGISTRATION NO.
(if appropriate)
Docket Number:

47,023

TELEPHONE 732-235-9350

NJMS-02-90

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Complete if Known

Application Number
Filing Date Herewith
First Named Inventor HANAUSKE-ABEL, Hartmut M.
Examiner Name
Group Art Unit
Attorney Docket No. NJMS-02-90

TOTAL AMOUNT OF PAYMENT (\$) 80.00

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FEE CALCULATION

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106 330	206 165	Design filing fee	
107 510	207 255	Plant filing fee	
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114 160	214 80	Provisional filing fee	80.00

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2. EXTRA CLAIM FEES

Total Claims	Extra Claims	Fee from below	Fee Paid
Independent	-20** =	X	
Multiple Dependent	-3** =	X	

Large Entity Fee Code (\$)	Small Entity Fee Code (\$)	Fee Description
103 18	203 9	Claims in excess of 20
102 84	202 42	Independent claims in excess of 3
104 280	204 140	Multiple dependent claim, if not paid
109 84	209 42	** Reissue independent claims over original patent
110 18	210 9	** Reissue claims in excess of 20 and over original patent

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3. ADDITIONAL FEES

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105 130	205 65	Surcharge - late filing fee or oath	
127 50	227 25	Surcharge - late provisional filing fee or cover sheet	
139 130	139 130	Non-English specification	
147 2,520	147 2,520	For filing a request for ex parte reexamination	
112 920*	112 920*	Requesting publication of SIR prior to Examiner action	
113 1,840*	113 1,840*	Requesting publication of SIR after Examiner action	
115 110	215 55	Extension for reply within first month	
116 400	216 200	Extension for reply within second month	
117 920	217 460	Extension for reply within third month	
118 1,440	218 720	Extension for reply within fourth month	
128 1,960	228 980	Extension for reply within fifth month	
119 320	219 160	Notice of Appeal	
120 320	220 160	Filing a brief in support of an appeal	
121 280	221 140	Request for oral hearing	
138 1,510	138 1,510	Petition to institute a public use proceeding	
140 110	240 55	Petition to revive - unavoidable	
141 1,280	241 640	Petition to revive - unintentional	
142 1,280	242 640	Utility issue fee (or reissue)	
143 460	243 230	Design issue fee	
144 620	244 310	Plant issue fee	
122 130	122 130	Petitions to the Commissioner	
123 50	123 50	Processing fee under 37 CFR 1.17(q)	
126 180	126 180	Submission of Information Disclosure Stmt	
581 40	581 40	Recording each patent assignment per property (times number of properties)	
146 740	246 370	Filing a submission after final rejection (37 CFR § 1.129(a))	
149 740	249 370	For each additional invention to be examined (37 CFR § 1.129(b))	
179 740	279 370	Request for Continued Examination (RCE)	
169 900	169 900	Request for expedited examination of a design application	

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Art Unit	:	None assigned	Docket No.	:	NJMS-02-90
Examiner	:	None assigned	Dated	:	November 8, 2002
Serial No.	:	Unknown			
Filed	:	Herewith			
Inventors	:	Hartmut M. Hanauske-Abel, et al.			
Title	:	"Small Molecule Ligands Of Eukaryotic Translation Initiation Factor 5A (eIF-5A) And Their Use to Control Proliferation Of Cells"			

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November 8, 2002
Date

**Small Molecule Ligands Of
Eukaryotic Translation Initiation Factor 5A (eIF-5A)
And Their Use to Control Proliferation Of Cells.**

The government has certain rights in this invention.

Abstract

We have identified eukaryotic translation initiation factor 5A (eIF-5A) as a non-enzymatic target for folate-derived agents that interfere with cell proliferation.

Background

The eukaryotic translation initiation factor 5A (eIF-5A), which exists in two genetically distinct variants, I and II, is involved in the translational control of gene expression. Compounds that affect the physiological structure of eIF-5A, in particular its lysine-derived hypusine residue, cause a unique subset of cellular mRNA's termed *hymns* (hypusine-dependent messenger nucleic acids) to disappear from cellular polysomes (1). This effect is associated with arrest in the late G1 phase of the cell cycle, immediately before the initiation of DNA replication (2).

Folate, a vitamin required for metabolism of one-carbon units and essential for the biosynthesis of DNA and RNA building blocks, is also known to be involved in the translational control of gene expression. For instance, whereas the levels of the mRNA encoding dihydrofolate reductase or of the mRNA encoding the folate receptor alpha do not change in response to alterations of folate levels, the translation of these mRNAs occur in a manner that is sensitive to the concentration of folate or folate analogs and antagonists (3,4).

Surprisingly, we noted that the eIF-5As display significant structural homologies with at least one of the proteins whose translational efficiency is affected by folate/antifolate levels: the dihydrofolate reductases (DHFRs).

Recent structural analyses of eIF-5A indicate that its C-terminal part folds like the cold-shock protein A of *E. coli*, (5), and that its most N-terminal part contains motifs II, III, IV, and V of ATP-utilizing mRNA helicases, required for unwinding of mRNA duplexes (6). Using the spatial coordinates of only the N-terminal part of eIF-5A of *M. jannaschii* (PDB# 1EIF), we noted a significant homology with the crystal structure of plasmid-encoded DHFR of *E. coli* (PDB# 1vie), using the Dali algorithm (Z score = 4.4)., See Figure 1

Similarly, optimized sequence alignment between human DHFR (Acc.# XM_165390) and the human eIF-5As (I: Acc.# NP_001961; II: Acc.# NP_065123) revealed 37% identify/similarity with eIF-5A-I and 35% identify/similarity with eIF-5A-II. The N-terminal domain of the human eIF-5As displays several isolated residues that in DHFR participate in binding of folate and the antifolate methotrexate (e.g. Ile⁷, Pro⁶¹, Arg⁷⁰), and of NADPH (e.g. Gly²⁰, Lys⁵⁴, Gly¹¹⁷, Ser¹¹⁸). Distinct sequence differences affecting residues involved in catalytic efficiency, such as the E30Q isolation, suggest the eIF-5As display limited if any DHFR activity, see Figure 2.

Based on the above background, we hypothesize that in eIF-5A, the DHFR-like structural motifs function in rendering the translational control of *hymns* sensitive to levels of folate and its analogs. The discovery within eIF-5As of substructures that are a prerequisite for binding of folate and of folate derivatives identifies the eIF-5As as potential targets for these small molecule ligands, and points to multiple applications in conditions that involve cell proliferation.

Detailed Description of the Invention

It is established that eIF-5A is directly involved in the cellular machinery that controls the onset of DNA replication and initiates proliferation of cells.

Surprisingly, we noted marked similarities between eIF-5A and dihydrofolate reductase at the level of their primary as well as their tertiary structures, involving in particular motifs that in the enzyme enable the binding of folate and its derivatives. eIF-5A and dihydrofolate reductase are both known to control translational efficiency of specific mRNAs, the latter in a manner controlled by the level of folate/antifolate.

For those knowledgeable in the art, the outlined results represent information directly enabling the use of folate and its derivatives, and the discovery and development of novel folate analogs, that modulate the translational control of gene expression executed by eIF-5A.

Examples

The examples are not intended to limit the invention.

Example 1: The Crystal Structure

Reactivation of DOHH causes rapid reappearance of *hymns* at polysomes and subsequent, highly synchronized entry of cells into S phase. The *hymns*, though encoding very diverse cell cycle-relevant proteins, share common nucleotide motifs, termed JSBs, in their untranslated 3'- and 5'-regions. Recent structural analyses of eIF-5A indicate that its C-terminal part folds like the cold-shock protein A of *E. coli*, which prevents mRNA duplex formation at low temperatures (*Structure* 6, 1207; 1998), and that human eIF-5As in their most N-terminal part contain motifs II, III, IV, and V of ATP-utilizing mRNA helicases, required for unwinding of mRNA duplexes (FASEB J 16, A549; 2002). Hypothesizing that eIF-5A crystal structure / sequence data contain further clues for its interaction with specific mRNAs essential for cell cycle control, we refined parameters and strategies of an exhaustive database analysis. Using the spatial coordinates of only the N-terminal part of eIF-5A of *M. jannaschii* (PDB# 1EIF), we noted a significant homology with the crystal structure of plasmid-encoded dihydrofolate reductase (DHFR) of *E. coli* (PDB# 1vie), using the Dali algorithm (Z score = 4.4), see Figure 1.

Example 2: Sequence Isolation

Optimized sequence alignment between human DHFR (Acc.# XM_165390) and the human eIF-5As (I: Acc.# NP_001961; II: Acc.# NP_065123) revealed 37% identify/similarity with eIF-5A-I and 35% identify/similarity with eIF-5A-II. The N-terminal domain of the human eIF-5As displays

several isolated residues that in DHFR participate in binding of folate and methotrexate (e.g. Ile7, Pro61, Arg70) and of NADPH (e.g. Gly20, Lys54, Gly117, Ser118), whereas distinct differences, such as the E30Q isolation, suggest limited DHFR activity, see Figure 2. **Example 3: Antibody Characterization**

The eukaryotic translation initiation factor 5A (eIF-5A) exists in two genetically distinct variants, I and II. Both contain a single hypusine residue, formed by enzymatic hydroxylation within a -Gly-X-Y-Gly- collagen motif known to fold into a β -turn. Like the collagens, the eIF-5As are subject to posttranslational protein hydroxylation by a 2-oxoacid-utilizing dioxygenase; the eIF-5A-hydroxylating enzyme is the hypusine-forming deoxyhypusyl hydroxylase (DOHH). The catalytic cycle of all 2-oxoacid-utilizing dioxygenases including DOHH, follows a unique pathway formulated by Hanauske-Abel and Günzler (1), which proceeds at their non-heme ferrous ion as a ligand reaction between a chelating 2-oxoacid moiety and an end-on coordinated dioxygen unit to generate the reactive iron-oxo species essential for product formation. The detailed orbital interactions specified by the HAG mechanism were essential for the rational discovery of inhibitors that suppress hypusine formation in eIF-5As, revealing an essential role in polysomal loading of specific mRNAs (*hymns*) and in the onset of DNA replication, i.e. exit from G1 (2,3). **Figure 3** shows the typical effect of a hypusine inhibitor on cellular DOHH activity (blue) and on cell cycle progression (red / black) [reproduced from ref. 3]. Thus, the eIF-5As and their unique hypusine residue appear closely related to, or even represent the molecular equivalent of, one of the major restriction points in the cell cycle: the irreversible commitment to initiate DNA replication. The hypusine domain of eIF-5A has emerged as the target for several experimental cytostatic agents and for antiproliferative drugs already in clinical use, among them the antifungal compound ciclopirox (4,5).

We recently characterized an antibody, NIH-353, as being reactive with human eIF-5A only if hypusine has been formed (**Figure 4A**). The hypusine residue is not genetically encoded; rather, it derives from a genetically encoded lysine moiety, after butylamine transfer utilizing spermidine, followed by the DOHH-mediated hydroxylation utilizing atmospheric oxygen (**Figure 4B**). Immunohistochemical analysis of human tissues and cancers has confirmed that the hypusine domain-selective NIH-353 labels only proliferating cells, as shown in **Figure 4C** for normal endometrium (proliferative phase) [compare with Ki67 control stain, **Figure 4D**].

Material and Methods

Protein structural alignments used the crystal coordinates of eIF-5A from *M.jannaschii* (PDB# 2EIF), the plasmid-encoded dihydrofolate reductase of *E.coli* (PDB# 1VIE and PDB# 1VIF), and the cold-shock protein of *E.coli* (PDB# 1MJC). Comparisons were performed with Dali v. 2. Molecules were visualized with InsightII. Linear alignments were generated with ClustalW and manually optimized.

Figures

One-dimensional (A,B) and three-dimensional (C) alignments of the N-terminal and the C-terminal part of archaeal eIF-5A with bacterial dihydrofolate reductase (bDHFR) and with bacterial cold shock protein A (csp-A).

The similarity between csp-A and the C-terminal part of eIF-5A has been observed before (7).

The N-terminal part of eIF-5A contains the lysine precursor of hypusine (A) and the β -turn of the hypusine domain (C), both highlighted in blue.

Note the red arrows in the linear (A) and in the steric (C) alignments. The bDHFR residue Gln51, whose planar terminal amide group sandwiches onto the the planar pterin moiety of folate (PDB #1vif), is iso-positioned with the eIF-5A residue Arg44, which also displays a similarly oriented, planar guanidinium group.

Figure 4A: Western blot of antibody

Figure 4B: Pathway

Figures 4C and 4D: Immunohistochemical analysis of human tissues and cancers

References

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Detection of a sub-set of polysomal mRNAs associated with modulation of hypusine formation at the G1-S boundary. Proposal of a role for eIF-5A in onset of DNA replication.
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Inhibition of the G1-S transition of the cell cycle by inhibitors of deoxyhypusine hydroxylation.
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3. Ercikan-Abali EA; Banerjee D; Waltham MC; Skacel N; Scotto KW; Bertino JR (1997)
Dihydrofolate reductase protein inhibits its own translation by binding to dihydrofolate reductase mRNA sequences within the coding region.
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4. Zhu WY; Alliegro MA; Melera PW (2001)
The rate of folate receptor alpha (FR alpha) synthesis in folate depleted CHL cells is regulated by a translational mechanism sensitive to media folate levels, while stable overexpression of its mRNA is mediated by gene amplification and an increase in transcript half-life.
J Cell Biochem **81**, 205 – 219
5. Peat TS; Newman J; Waldo GS; Berendzen J; Terwilliger TC (1998)
Structure of translation initiation factor 5A from *Pyrobaculum aerophilum* at 1.75 Å resolution.
Structure **6**, 1207-1214
6. HM Hanauske-Abel, A R Hanauske, B Slowinska, A M Popowicz (2002)
The cell cycle-controlling protein eIF-5A : Identification of functional regions relevant for interaction with its mRNA partners.
FASEB J. **16**, A549

We claim the following :

1. A ligand specific for the folate-binding domain of eukaryotic translation initiation factor 5A (eIF-5A), said folate-binding domain being defined as composed of residue motifs common to eIF-5A and to the bacterial and human dihydrofolate reductases as shown in Figure 2, and said ligand being characterized as binding to the folate-binding domain of eIF-5A.
2. A ligand as claimed in Claim 1 in which the ligand is an analog of folate, or a derivative or fragment thereof, which specifically binds to an eIF-5A molecule only if said eIF-5A contains a folate-binding domain, and if eIF-5A lacks said domain does not bind.
3. A method for identifying a novel class of folate derivatives that are inhibitors of proliferation yet do not inhibit folate-dependent enzymes.
4. A method for independent inhibiting in a cell the biological activity of the folate-binding domain of eIF-5A as composed of residue motifs identified in Figure 2, comprising introducing into said cell a low-molecular weight molecule that binds to the folate-binding domain of eIF-5A to thereby inhibit the biological activity of eIF-5A in the translational control of gene expression required for cell proliferation.

Figure 1

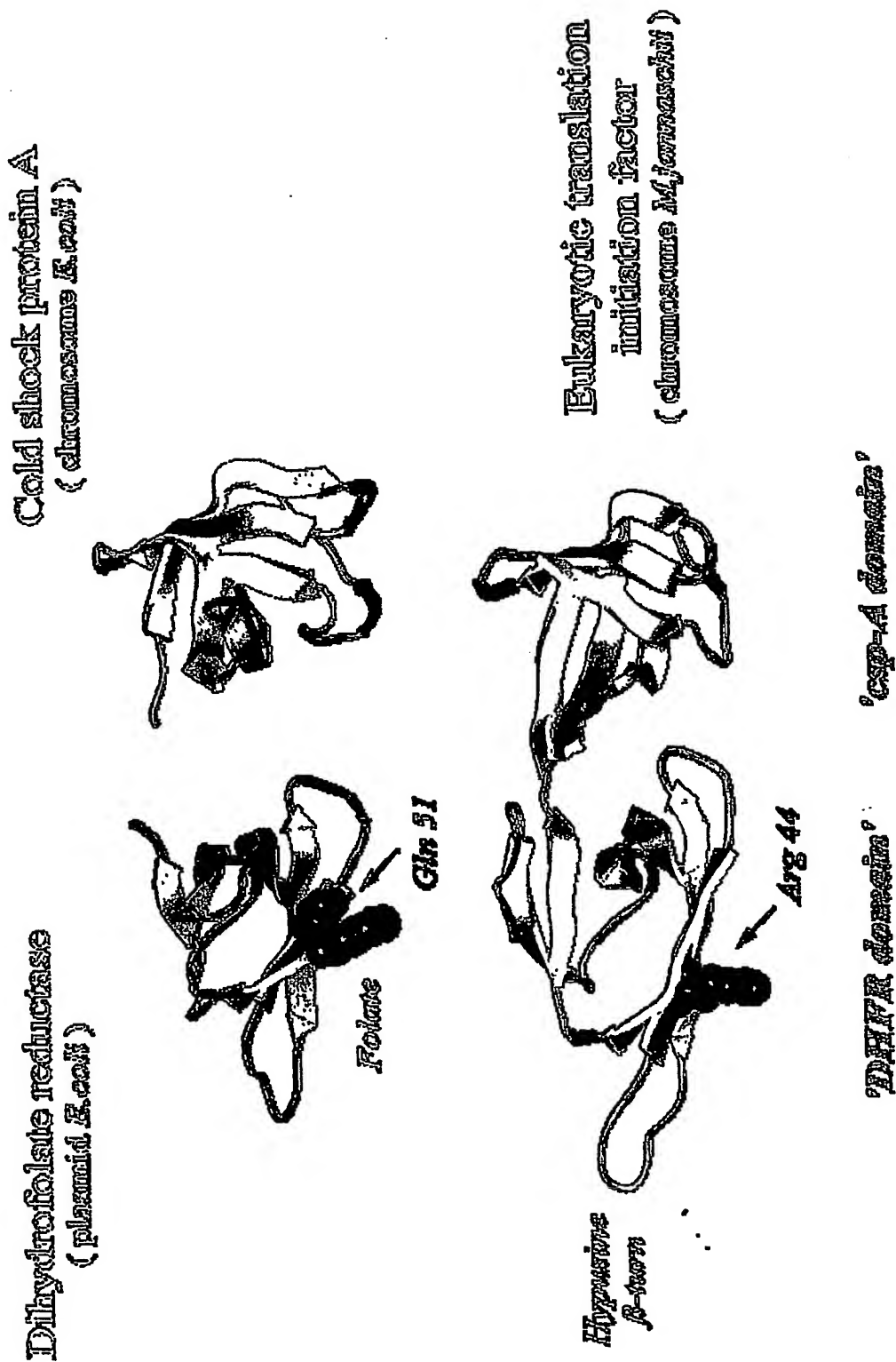


Figure 3

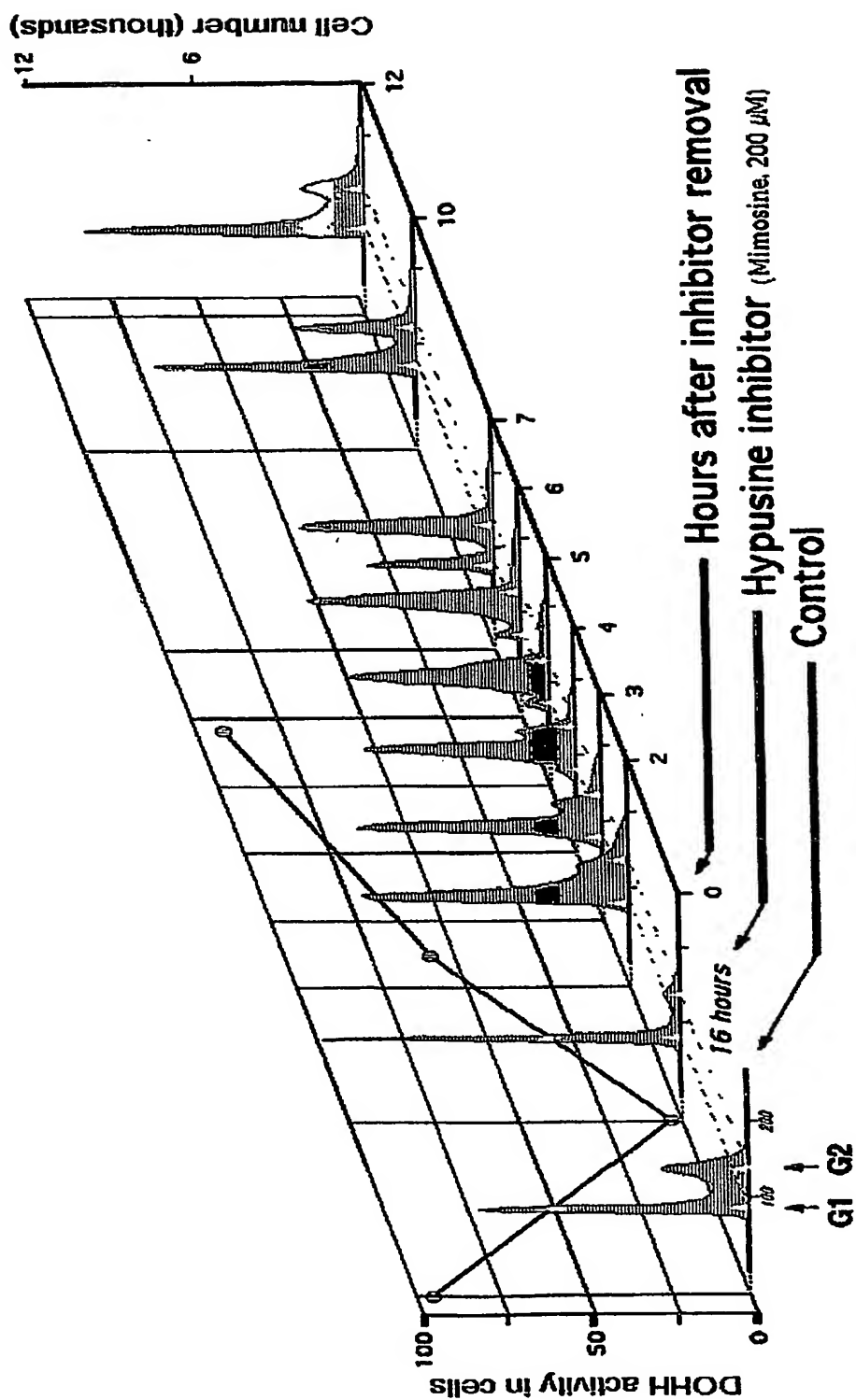
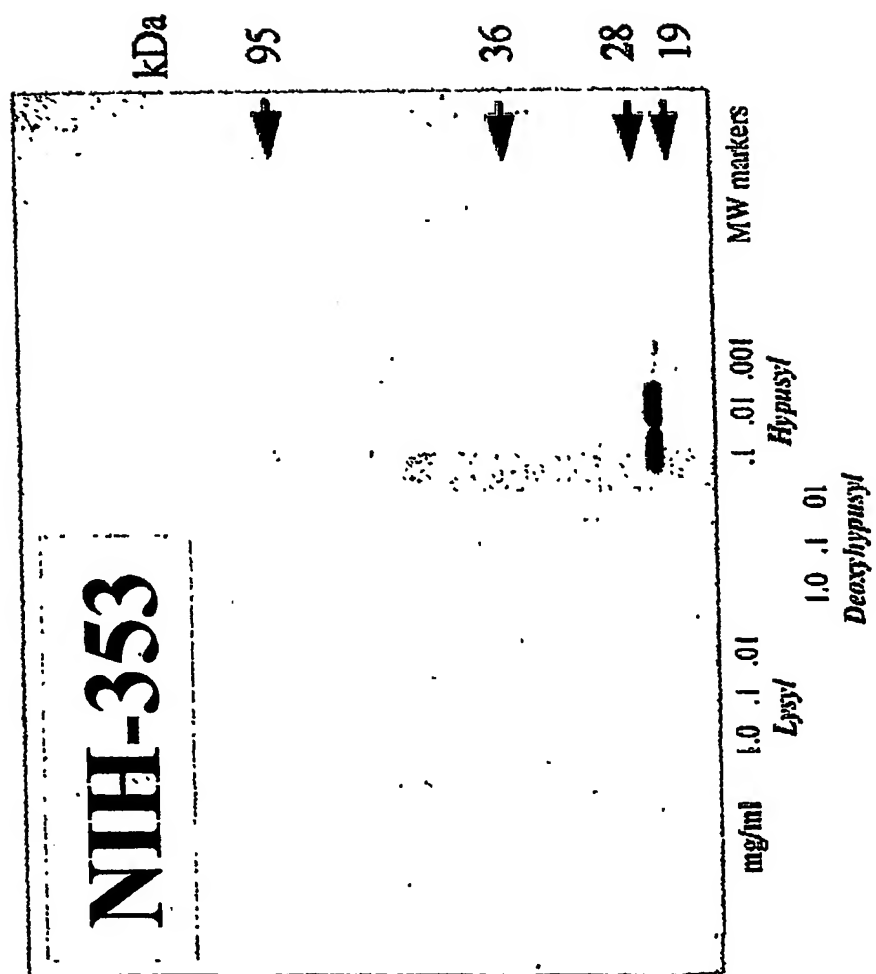


Figure 4A



MW markers

100' 10' 1"

Hypusyl

19101

Deoxyhypusyl

mg/ml 10 1 0.1

1857

kDa

95

36

28

19

Figure 4B

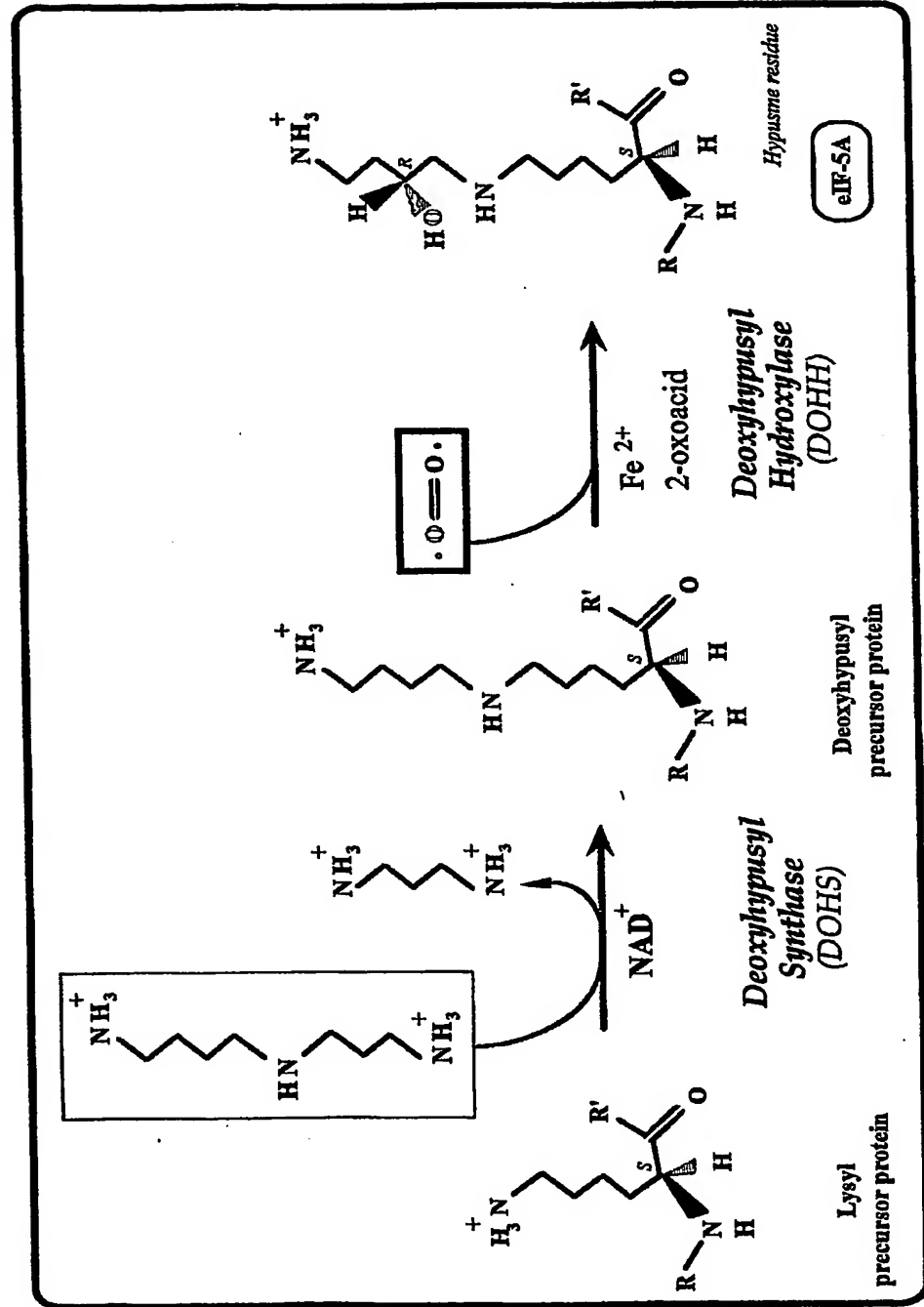


Figure 4C

NIH-353

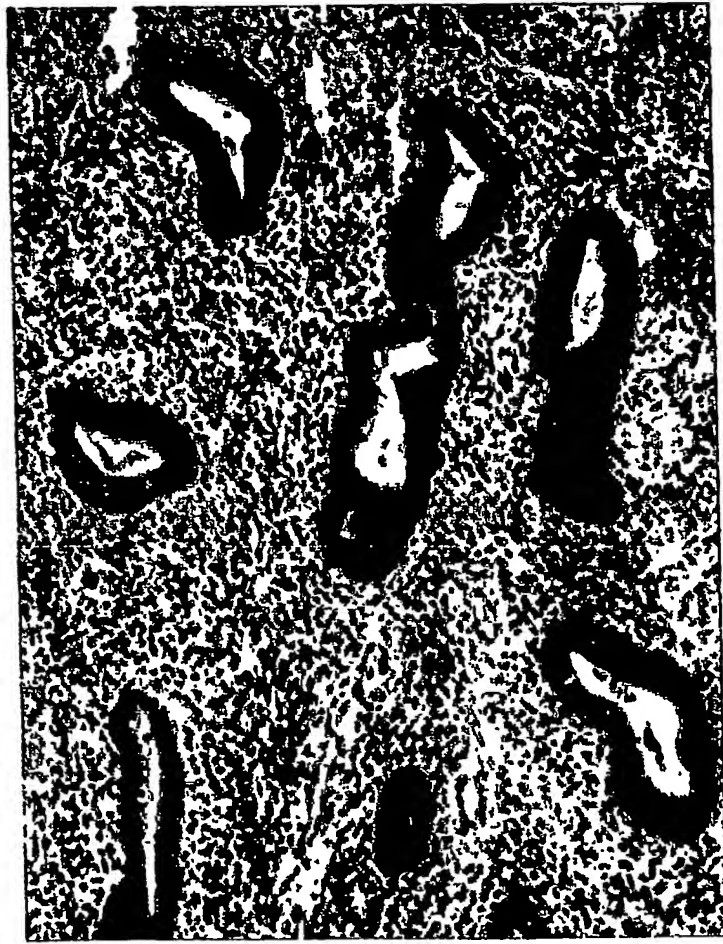


Figure 4D



Ki-67 control

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